

University of Groningen

Safety Communication Tools and Healthcare Professionals' Awareness of Specific Drug Safety Issues in Europe
SCOPE Work Package 6

Published in:
Drug Safety

DOI:
[10.1007/s40264-018-0643-5](https://doi.org/10.1007/s40264-018-0643-5)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2018

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

SCOPE Work Package 6 (2018). Safety Communication Tools and Healthcare Professionals' Awareness of Specific Drug Safety Issues in Europe: A Survey Study. *Drug Safety*, 41(7), 713-724.
<https://doi.org/10.1007/s40264-018-0643-5>

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de Vries, S. T., van der Sar, M. J. M., Coleman, A. M., Escudero, Y., Rodríguez Pascual, A., Maciá Martínez, M-Á., ... SCOPE work package 6 (2018). Safety Communication Tools and Healthcare Professionals' Awareness of Specific Drug Safety Issues in Europe: A Survey Study. *Drug Safety*. DOI: 10.1007/s40264-018-0643-5

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Safety Communication Tools and Healthcare Professionals' Awareness of Specific Drug Safety Issues in Europe: A Survey Study

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Abstract

Introduction National competent authorities (NCAs) use Direct Healthcare Professional Communications (DHPCs) to communicate new drug safety issues to healthcare professionals (HCPs). More knowledge is needed about the effectiveness of DHPCs and the extent to which they raise awareness of new safety issues among HCPs.

Objective The objective was to assess and compare general practitioners' (GPs'), cardiologists', and pharmacists' familiarity with DHPCs as communication tools, their awareness of specific drug safety issues, and the sources through which they had become aware of the specific issues.

The other members of SCOPE work package 6 are listed in Acknowledgements.

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s40264-018-0643-5>) contains supplementary material, which is available to authorized users.

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Methods GPs, cardiologists, and pharmacists from nine European countries (Croatia, Denmark, Ireland, Italy, the Netherlands, Norway, Spain, Sweden, and the UK) completed a web-based survey. The survey was conducted in the context of the Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) Joint Action. Respondents were asked about their familiarity with DHPCs in general and their awareness of safety issues that had recently been communicated and involved the following drugs: combined hormonal contraceptives, diclofenac, valproate, and ivabradine. Those HCPs who were aware of the specific safety issues were subsequently asked to indicate the source through which they had become aware of them. Differences between professions in familiarity with DHPCs and awareness were tested using a Pearson χ^2 test per country and post hoc Pearson χ^2 tests in the case of statistically significant differences.

Results Of the 3288 included respondents, 54% were GPs, 40% were pharmacists, and 7% were cardiologists. The number of respondents ranged from 67 in Denmark to 916 in Spain. Most respondents (92%) were familiar with DHPCs, with one significant difference between the professions: pharmacists were more familiar than GPs in Italy (99 vs 90%, $P = 0.004$). GPs' awareness ranged from 96% for the diclofenac issue to 70% for the ivabradine issue. A similar pattern was shown for pharmacists (91% aware of the diclofenac issue to 66% of the ivabradine issue). Cardiologists' awareness ranged from 91% for the ivabradine issue to 34% for the valproate issue. Overall, DHPCs were a common source through which GPs (range: 45% of those aware of the contraceptives issue to 60% of those aware of the valproate issue), cardiologists (range: 33% for the contraceptives issue to 61% for the valproate issue), and pharmacists (range: 41% for the contraceptives issue to 51% for the ivabradine issue) had become aware of the

specific safety issues, followed by information on websites or in newsletters.

Conclusions GPs, cardiologists, and pharmacists were to a similar extent (highly) familiar with DHPCs, but they differed in awareness levels of specific safety issues. Cardiologists were less aware of safety issues associated with non-cardiology drugs even if these had cardiovascular safety concerns. This implies that additional strategies may be needed to reach specialists when communicating safety issues regarding drugs outside their therapeutic area but with risks related to their field of specialisation. DHPCs were an important source for the different professions to become aware of specific safety issues, but other sources were also often used. NCAs should consider the use of a range of sources when communicating important safety issues to HCPs.

Key Points

Familiarity with Direct Healthcare Professional Communications (DHPCs) was high among general practitioners (GPs), cardiologists, and pharmacists across Europe.

Cardiologists were more aware than GPs of the safety issue for a drug within their field of expertise (ivabradine) and less aware than GPs and pharmacists of safety issues of other drugs (contraceptives, diclofenac, and valproate), despite some of these relating to cardiovascular risks.

DHPCs were an important source for GPs, cardiologists, and pharmacists to become aware of specific safety issues, but other sources, such as websites or newsletters and medical journals, were also relevant.

1 Introduction

There have been some high-profile drug safety issues in recent years where re-evaluation of the risks associated with drugs such as rosiglitazone and sibutramine led to their removal from the market by European regulators as the benefit–risk balance was judged to be negative [1, 2]. More often, however, important new safety issues emerge where the overall benefit–risk balance of the drug remains positive provided healthcare professionals (HCPs) take into account certain warnings and precautions and the drug remains on the market. In these cases, national competent

authorities (NCAs) inform HCPs about these risks and the actions that they should take to minimise or manage them. Research, however, has shown that the safety advice in communications from regulators is not always followed [3–5]. Before HCPs can act on a safety issue, they first need to become aware of it. A study published in 2012 among a sample of Dutch HCPs showed mixed awareness of drug safety issues, ranging from 56% of HCPs being aware of new safety issues with etoricoxib up to 88% for clopidogrel [6]. Moreover, it was shown that awareness varied among professions, where pharmacists were generally more aware of safety issues than general practitioners (GPs) [6].

Direct Healthcare Professional Communications (DHPCs) are an important tool that NCAs use to communicate new drug safety information to HCPs [7]. DHPCs are letters predominantly distributed by pharmaceutical companies following content approval by the NCAs. Some research suggests that about one-fifth of HCPs are not familiar with these communications. Again, differences between professions were seen, with GPs being more familiar with these communications than pharmacists [6]. Besides DHPCs, NCAs can use additional tools to raise awareness of safety issues, such as the NCA's own communications (e.g. newsletters) [7]. Currently, it is not known how HCPs become aware of safety issues (i.e. via DHPCs or other sources) and whether this differs between professions. A previous study showed that NCAs from European countries generally use similar methods for safety communication, but that GPs' awareness of safety communication tools differ across countries [8].

The aim of this study was to expand the current knowledge about differences between professions in familiarity with DHPCs and awareness of safety issues in various European countries. More specifically, our aims were to compare GPs, cardiologists, and pharmacists regarding their familiarity with DHPCs, their awareness of specific recent drug safety issues, and the sources through which they have become aware of these issues. This knowledge is important for NCAs in the evaluation of their current safety communication strategies and to facilitate improvement in the future. Knowing how different professions perceive current drug safety communication tools and the sources they used most in informing themselves of important updates can help NCAs to optimise their safety communication strategies.

2 Methods

2.1 Study Design and Data Collection

Cross-sectional data from a web-based survey about HCPs' views and experiences regarding drug safety information

were used for this study. The data were collected in the year 2015 in the context of the Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) Joint Action Work Package 6 (<http://www.scopejointaction.eu/>). The active partners in this work package developed the survey in the English language (see Electronic Supplementary Material 1). This survey was translated by an official translation agency in the following languages: Croatian, Danish, Dutch, Italian, Norwegian, Spanish, and Swedish. Thereafter, the surveys were back-translated and pilot tested to check whether the translations had the same meaning as the English version and whether the survey was understandable for people not involved in the project. Unipark software (<http://www.unipark.com/en/>) was used to create the web-based format of the survey. Ethical approval was not considered necessary because of the nature of the study, in which HCPs were asked to complete a survey about safety communication strategies.

2.2 Participants

The survey was distributed among HCPs in nine European countries that were active partners in Work Package 6 of the Joint Action; i.e. Croatia, Denmark, Ireland, Italy, the Netherlands, Norway, Spain, Sweden, and the UK. HCPs were recruited via a link to the survey on websites, in newsletters, and/or in an email sent by the NCA, a professional body, or a commercial organisation to all their subscribers or members. HCPs that were actively targeted and included in this study were GPs, cardiologists, and pharmacists. In Spain and Sweden, only GPs and cardiologists were actively targeted.

2.3 Outcome Assessment

To assess HCPs' familiarity with DHPCs the survey contained a short introduction about DHPCs with two examples pictured, after which respondents were asked the following closed-ended question: "Are you familiar with this type of safety communication?" Respondents answering "Yes" were considered familiar, whereas respondents answering "No, I have heard of DHPCs, but I have never seen one" or "No, I have never heard of DHPCs" were considered unfamiliar with DHPCs.

HCPs' awareness of specific safety issues was assessed using the following question: "Are you aware of updates to the safety profiles of the following medicines?" The presented drug safety issues were updates on the risk of thrombosis with combined hormonal contraceptives (contraceptives), cardiovascular harms with diclofenac, teratogenicity with valproate, and cardiovascular events with ivabradine (Table 1). These safety issues were chosen as they had been the subject of NCA safety communications

in the period just prior to the survey being conducted [following review within safety referral procedures by the Pharmacovigilance Risk Assessment Committee (PRAC)], and to have a representative sample of drugs used in primary care (contraceptives and diclofenac) along with specialised care (valproate and ivabradine). The safety issue for ivabradine was not included in the Norwegian survey because this drug is not on the market in Norway.

Finally, when respondents indicated that they were aware of a certain safety issue, they were asked how they had heard about it. The source options provided were as follows: via a DHPC, a website or newsletter, educational materials, a professional body, a colleague, a medical journal, lay media (newspaper/television), or other source. The Norwegian survey included an additional answer option, i.e. through the national medicines agency. It was possible to provide multiple answers on how HCPs became aware of the safety issues.

2.4 Analyses

Descriptive information about the included population is presented as frequencies with percentages for the total population and per profession.

HCPs' familiarity with DHPCs and awareness of each of the four specific safety issues are presented as percentages per profession within each country. Only HCPs who were familiar with DHPCs were included in the assessment of awareness of the safety issues. Differences in familiarity with DHPCs and awareness between professions were tested using a Pearson χ^2 test per country. In the case of a statistically significant result (P value of <0.05), Pearson χ^2 tests were used to assess which professions differed from each other. A Bonferroni adjustment to correct for multiple testing ($N = 3$) was used for these post hoc tests, implying that a P value of <0.016 was considered statistically significant.

Data from the sources through which the HCPs heard of the safety issues were analysed descriptively. The results of these analyses are presented per profession using percentages per safety issue and per country for those HCPs who were aware of the safety issue. The additional answer option in the Norwegian survey was classified as "other" sources.

All analyses were conducted using Stata version 13 (Stata Corp., College Station, TX, USA), and Microsoft Excel 2010 was used for the graphical presentation of the results.

3 Results

In total, 3625 HCPs completed the survey, of whom 337 had a profession different than the target population of GPs, cardiologists, and pharmacists. Of the remaining 3288

Table 1 Summary of the drugs for which the safety updates were assessed in this study

Characteristic	Combined hormonal contraceptives	Diclofenac	Valproate	Ivabradine
Indicated for/treatment of	Contraception	Relieving pain and inflammation	Generalised, partial or other epilepsy; bipolar disorder	Symptomatic treatment of chronic stable angina pectoris. Treatment of chronic heart failure
Most common prescriber	GPs	GPs	Neurologists, psychiatrists	Cardiologists
New safety information	Risk of VTE. Confirmation that the absolute risk of VTE with all CHCs is small and ranges from 5 to 12 cases of VTE per 10,000 women per year, but that differences exist depending on the type of progestogen they contain and for a given dose of oestrogen, with levonorgestrel, norethisterone or norgestimate (so called second generation) having the lowest risk as per the available evidence	Risk of cardiovascular events. The same cardiovascular precautions now apply for diclofenac as for selective COX-2 inhibitors, i.e. 'coxibs'	Risk of teratogenicity. Further characterisation of the teratogenic effects: children exposed in utero are at a high risk of serious developmental disorders (in up to 30–40% of cases) and/or congenital malformations (in approximately 10% of cases)	Risk of cardiovascular events. A small but significant increase of the combined risk of cardiovascular death, myocardial infarction, and cardiac failure was seen in patients with symptomatic angina [9]
Implications of the new safety information	Careful consideration to be given to the new evidence when prescribing CHCs in addition to emphasising existing contraindications for use and evaluating the individual woman's current risk factors for VTE	Use contraindicated in ischaemic heart disease, peripheral arterial disease, cerebrovascular disease, and congestive heart failure. Careful consideration to be given to an individual's risk factors for cardiovascular events before prescribing (e.g. hypertension, diabetes, hyperlipidaemia, and smoking)	Valproate should not be used in female children/adolescents of childbearing potential or pregnant women unless other treatments are ineffective or not tolerated. It must be started and supervised by a doctor experienced in managing epilepsy or bipolar disorder. All female patients must be informed of and fully understand the risks of use during pregnancy	Ivabradine is indicated only for symptomatic treatment of chronic stable angina pectoris because ivabradine has no benefits on cardiovascular outcomes (e.g. myocardial infarction or cardiovascular death) in patients with symptomatic angina. Serial heart rate measurements are required prior to initiation of therapy or prior to dose titration. Concomitant use with verapamil or diltiazem is contraindicated. Treatment should only be initiated in patients with a resting heart rate of at least 70 bpm
Year of DHPC	2014	2013	2014	2014
Distribution of DHPC per country				
<i>Format</i>				
Croatia	Hardcopy, point-of-care alerts for HCPs at primary level, NCA website and newsletter	Hardcopy, point-of-care alerts for HCPs at primary level, NCA website and newsletter	Hardcopy, point-of-care alerts for HCPs at primary level, NCA website and newsletter	Hardcopy, point-of-care alerts for HCPs at primary level, NCA website and newsletter
Denmark	Electronic and NCA website	Hardcopy and NCA website	Hardcopy and NCA website	Hardcopy and NCA website
Ireland	Hardcopy letter (also published on NCA website and article included in electronic NCA newsletter)	Hardcopy letter (also published on NCA website and article included in electronic NCA newsletter)	Hardcopy letter (also published on NCA website and article included in electronic NCA newsletter)	Hardcopy letter (also published on NCA website and article included in electronic NCA newsletter)
Italy	Hardcopy and NCA website	Hardcopy and NCA website	Hardcopy and NCA website	Hardcopy and NCA website
Netherlands	Hardcopy, NCA website and NCA newsletter	Hardcopy, NCA website and NCA newsletter	Hardcopy, NCA website and NCA newsletter	Hardcopy, NCA website and NCA newsletter
Norway	Hardcopy and point-of-care-alerts	Hardcopy and point-of-care-alerts	Hardcopy and point-of-care-alerts	N/A

Table 1 continued

Characteristic	Combined hormonal contraceptives	Diclofenac	Valproate	Ivabradine
Spain	Electronic and NCA website	Electronic and NCA website	Electronic and NCA website	Electronic and NCA website
Sweden	Hardcopy and NCA website	Hardcopy and NCA website	Hardcopy and NCA website	Hardcopy and NCA website
UK	Electronic cascade distribution and NCA website	Hardcopy letter and NCA website	Electronic cascade distribution and NCA website	Hardcopy letter and NCA website
<i>Targeted HCPs</i>				
Croatia	Gynaecologists, GPs, pharmacists, selected learned societies, hospitals' medicines committees	Internists, rheumatologists, GPs, pharmacists	Neurologists, psychiatrists, gynaecologists, GPs, pharmacists, selected learned societies, hospitals' medicines committees	Cardiologists, internists, GPs, selected learned societies, hospitals' medicines committees
Denmark	Danish medical societies, GPs association, Danish medical association, medical society for gynaecology and obstetrics	GPs, pharmacists, internists, rheumatologists	GPs, neurologists, psychiatrists, paediatricians, clinical pharmacologists, industrial medical officers, medical societies for neurology, psychiatry and clinical pharmacology, patient societies for epilepsy and psychiatry	GPs, cardiologists, internists in cardiology departments, medical societies for cardiology and GPs, Danish Heart Association
Ireland	GPs, family planning clinics, pharmacists, obstetricians, gynaecologists	GPs, all consultants (specialists), pharmacists, dentists	Neurologists, psychiatrists, GPs, obstetricians, gynaecologists, family planning centres, pharmacists, relevant HCP professional organisations	GPs, cardiologists, geriatricians, general medicine consultants, pharmacists
Italy	Gynaecologists, emergency room physicians, pneumologists, cardiologists, haematologists, hospital pharmacists, relevant scientific and HCP organisations/patient organisations	GPs, internists, cardiologists, rheumatologists, orthopaedics, geriatrics, pharmacists	Neurologists, psychiatrists, GPs, obstetricians/ gynaecologists, family planning centres, midwife, pharmacists (community and hospital), relevant scientific and HCP organisations/patient organisations	Internists, cardiologists, GPs, relevant learned societies
Netherlands	GPs, gynaecologists, pharmacists, hospital pharmacists	GPs, rheumatologists, internists, pharmacists, hospital pharmacists, orthopaedics	Neurologists, psychiatrists, gynaecologists, paediatricians and paediatric nurses, obstetricians, pharmacists	Cardiologists, GPs, hospital pharmacists
Norway	GPs, pharmacists, gynaecologists, midwives, public health nurses, emergency medical services, hospital surgical and internal medicine wards	GPs, pharmacists, internists, rheumatologists, surgeons, orthopaedists, emergency medical services	GPs, pharmacists, gynaecologists, neurologists, psychiatrists, midwives, industrial medical officers	N/A
Spain	GPs, gynaecologists, clinical pharmacologists, community pharmacists, PhV centres	GPs, geriatricians, internal medicine specialists, rheumatologists, traumatologists, rehabilitation specialists, pharmacists (community and hospital), PhV centres	Psychiatrists, neurologists, GPs, paediatricians, clinical pharmacologists, pharmacists (community and hospital), PhV centres	Cardiologists, GPs, internal medicine specialists, geriatricians, clinical pharmacologists, pharmacists (community and hospital), PhV centres

Table 1 continued

Characteristic	Combined hormonal contraceptives	Diclofenac	Valproate	Ivabradine
Sweden	GPs, gynaecologists, midwives	GPs, specialists in internal medicine (including rheumatologists and cardiologists), orthopaedist, pharmacies, county council drug committees	Neurologists, psychiatrists, gynaecologists, specialists in internal medicine, learned societies (neurology, epilepsy, psychiatry), county council drug committees	Cardiologists, specialists in internal medicine, GPs
UK	GPs, family planning clinics, nurses, gynaecologists, all pharmacists (community and hospital), midwives	GPs, retail pharmacists, chief pharmacists in secondary care, dentists in practice, dentists in mainstream hospitals, dental hospitals	GPs, pharmacists (community and hospital), secondary care	GPs, internal medicine specialists, cardiologists, chief pharmacists
<i>Sender of the DHPC</i>				
Croatia	MAH	MAH	MAH	MAH
Denmark	NCA	MAH	MAH	MAH
Ireland	MAH	MAH	MAH	MAH
Italy	MAH	MAH	MAH	MAH
Netherlands	MAH	MAH	MAH	MAH
Norway	MAH	MAH	MAH	N/A
Spain	Learned societies of targeted HCPs	Learned societies of targeted HCPs	Learned societies of targeted HCPs	Learned societies of targeted HCPs
Sweden	MAH	MAH	MAH	MAH
UK	NCA	MAH	NCA	MAH

CHCs combined hormonal contraceptives, *COX* cyclo-oxygenase, *DHPC* Direct Healthcare Professional Communication, *GP* general practitioner, *HCP* healthcare professional, *MAH* marketing authorisation holder, *N/A* not applicable, *NCA* national competent authority, *PhV* pharmacovigilance, *VTE* venous thromboembolism

respondents, 54% were GPs, 40% were pharmacists, and 7% were cardiologists (Fig. 1). The number of respondents ranged from 67 in Denmark to 916 in Spain. Most of the GPs, cardiologists, and pharmacists were from, respectively, Spain ($N = 847$), Italy ($N = 63$), and Norway ($N = 381$) (Fig. 2). More than half of the respondents per country were female, except for Italy (42% female) and the Netherlands (31% female) (see Electronic Supplementary Material 2).

3.1 Familiarity with DHPCs

Most respondents (92%) were familiar with DHPCs, and in general there were only small differences between GPs, cardiologists, and pharmacists in terms of their familiarity (Fig. 3). Only in Italy a significant difference between the professions was shown ($P = 0.016$). More pharmacists were familiar with DHPCs than GPs (99 vs 90%, $P = 0.004$). Familiarity was highest in Ireland, Italy, Spain, and the UK, where more than 90% of the GPs, cardiologists, and pharmacists were familiar with DHPCs. Familiarity was lowest for some professions in Sweden (i.e.

GPs), Croatia (i.e. cardiologists), and Norway (i.e. pharmacists).

3.2 Awareness of the Four Specific Safety Issues

Overall, GPs were most aware of the safety issue concerning diclofenac (96%), followed by contraceptives (88%), valproate (76%), and ivabradine (70%). The same pattern was shown for the pharmacists, with highest awareness of diclofenac (91%), followed by contraceptives (90%), valproate (80%), and ivabradine (66%). For the cardiologists, the pattern was different, with highest awareness of the ivabradine safety issue (91%), followed by diclofenac (79%), contraceptives (61%), and valproate (34%).

Cardiologists were significantly less aware of the contraceptives safety issue than GPs and/or pharmacists in six countries (i.e. Denmark, Italy, the Netherlands, Norway, Spain, and the UK) (Fig. 4a). In three countries (i.e. Spain, Italy, and Norway), they were also less aware of the diclofenac issue (Fig. 4b). For the valproate issue, cardiologists were less aware than GPs and/or pharmacists in

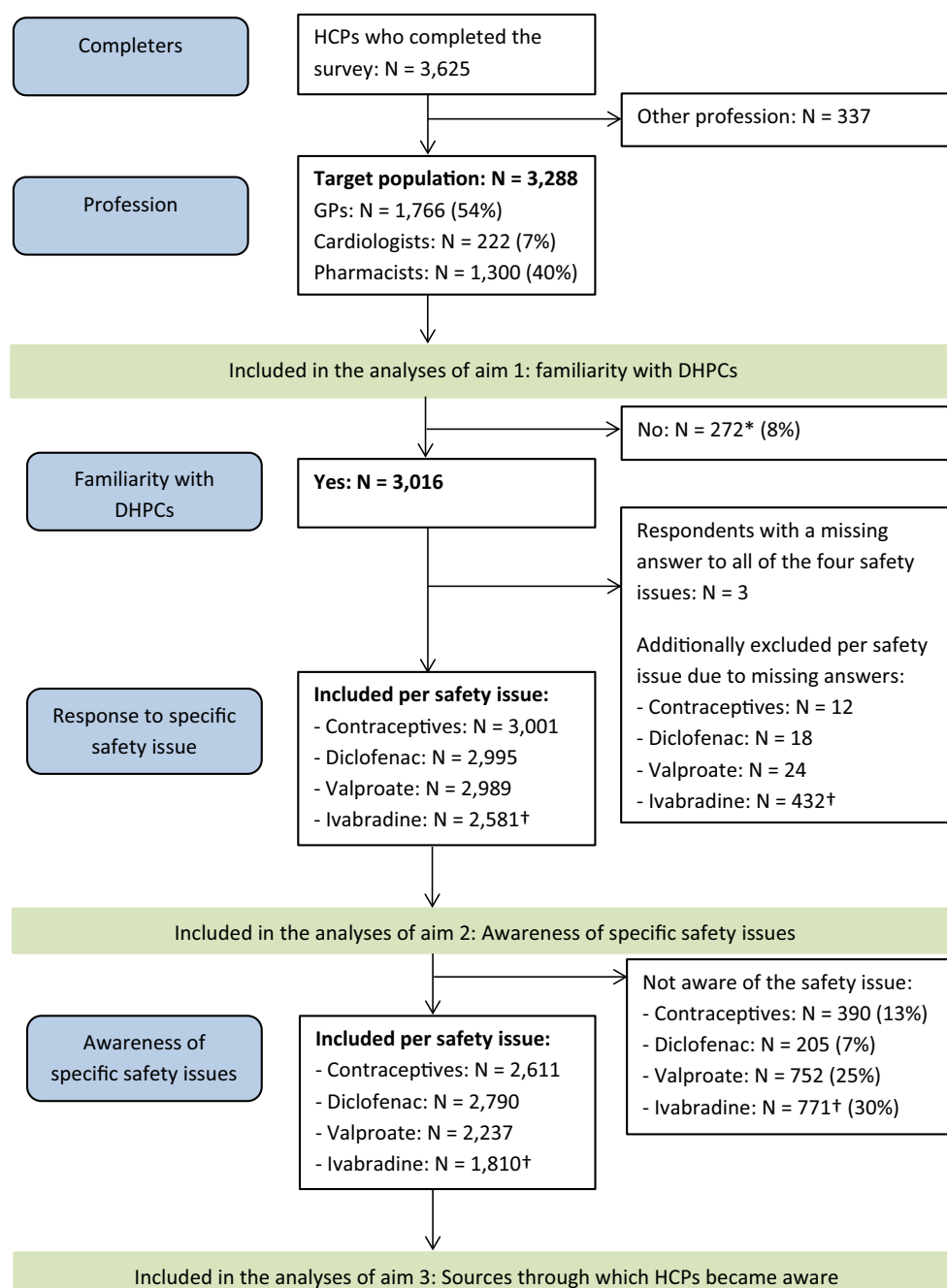


Fig. 1 Flowchart of number of healthcare professionals (HCPs) included per study aim. *272 responding HCPs were excluded: 135 had heard of Direct Healthcare Professional Communications

(DHPCs), but had never seen one; 136 had never heard of DHPCs; and 1 skipped the question. †This safety issue was not included in the survey in Norway. GPs general practitioners

five countries (i.e. Italy, the Netherlands, Norway, Spain, and the UK) (Fig. 4c). In Sweden, GP awareness of the valproate issue was low and cardiologists were more aware of this safety issue; respectively, 38 vs 69%, $P = 0.033$. For the ivabradine issue, cardiologists were more aware than GPs in four countries (i.e. Croatia, the Netherlands, Sweden, and the UK) (Fig. 4d).

Some differences between GPs and pharmacists were also observed (Fig. 4). Pharmacists were more aware of the contraceptives' safety issue than GPs (Croatia 96 vs 83%, $P = 0.003$; Italy 97 vs 88%, $P = 0.009$). They were also more aware of the ivabradine issue (Netherlands 56 vs 21%, $P < 0.001$). An inconsistent pattern across the countries was shown for the diclofenac and valproate issue. For the diclofenac issue, pharmacists were more aware than

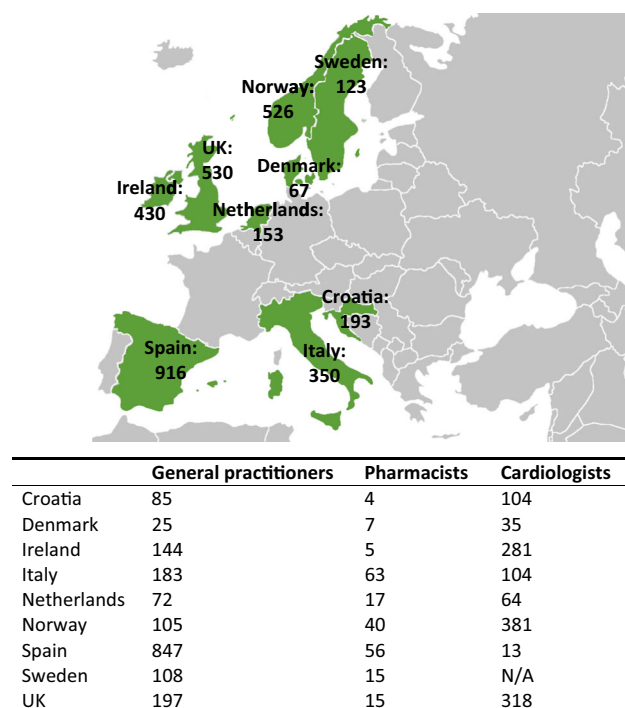


Fig. 2 Total number of respondents and per profession by country

GPs in the UK (99 vs 95%, $P = 0.009$), but less aware in Ireland (83 vs 93%, $P = 0.006$). For the valproate issue, pharmacists were more aware than GPs in Ireland (90 vs 65%, $P < 0.001$), in the UK (86 vs 68%, $P < 0.001$), and in the Netherlands (69 vs 45%, $P = 0.006$), but they were less aware in Norway (66 vs 81%, $P = 0.008$).

3.3 Sources

Most of the GPs who were aware of a specific safety issue indicated that they had heard about this through a DHPC (range: 45% of those aware of the contraceptives issue to 60% of those aware of the valproate issue), followed by a

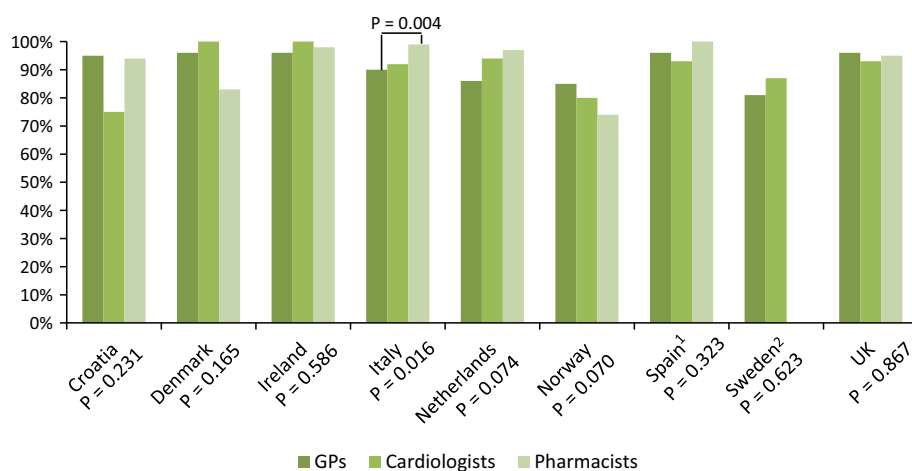
message on a website or in a newsletter (range: 37% of those aware of the valproate issue to 39% of those aware of the other issues) (see Electronic Supplementary Material 3). For many cardiologists, DHPCs were also mentioned as an important source (range: 33% for the contraceptives issue to 61% for the valproate issue), but in addition, medical journals were often mentioned for the contraceptives issue (46%), ivabradine issue (42%), and diclofenac issue (34%). A message on a website or in a newsletter was the source for 20% (contraceptives issue) to 30% (valproate issue) for the cardiologists. The sources most often mentioned by pharmacists were DHPCs (range: 41% for the contraceptives issue to 51% of the ivabradine issue) and information on a website or in a newsletter (range: 42% for the contraceptives and valproate issues to 46% for the diclofenac and ivabradine issues).

There was variation across the countries in the sources through which HCPs had become aware of the safety issues (see Electronic Supplementary Material 3). For instance, information provided by professional bodies was more often the source for HCPs in the Netherlands than for HCPs in the other countries. Another example is the “other” source through which somewhat more HCPs from Norway became aware of the issues compared to the number of HCPs from other countries. This other source contained the NCA’s own information centre, which was only specifically evaluated in the Norwegian survey. More HCPs from Italy became aware through a DHPC than did HCPs from other countries.

4 Discussion

This study shows that most GPs, cardiologists, and pharmacists across Europe are familiar with DHPCs. In general, GPs and pharmacists were more aware of the safety issues concerning contraceptives and diclofenac than

Fig. 3 Familiarity with Direct Healthcare Professional Communications (DHPCs) by profession per country. ¹Despite not being targeted, a few pharmacists from Spain completed the survey. ²In Sweden, pharmacists were not actively targeted and no pharmacists completed the survey. *GPs* general practitioners



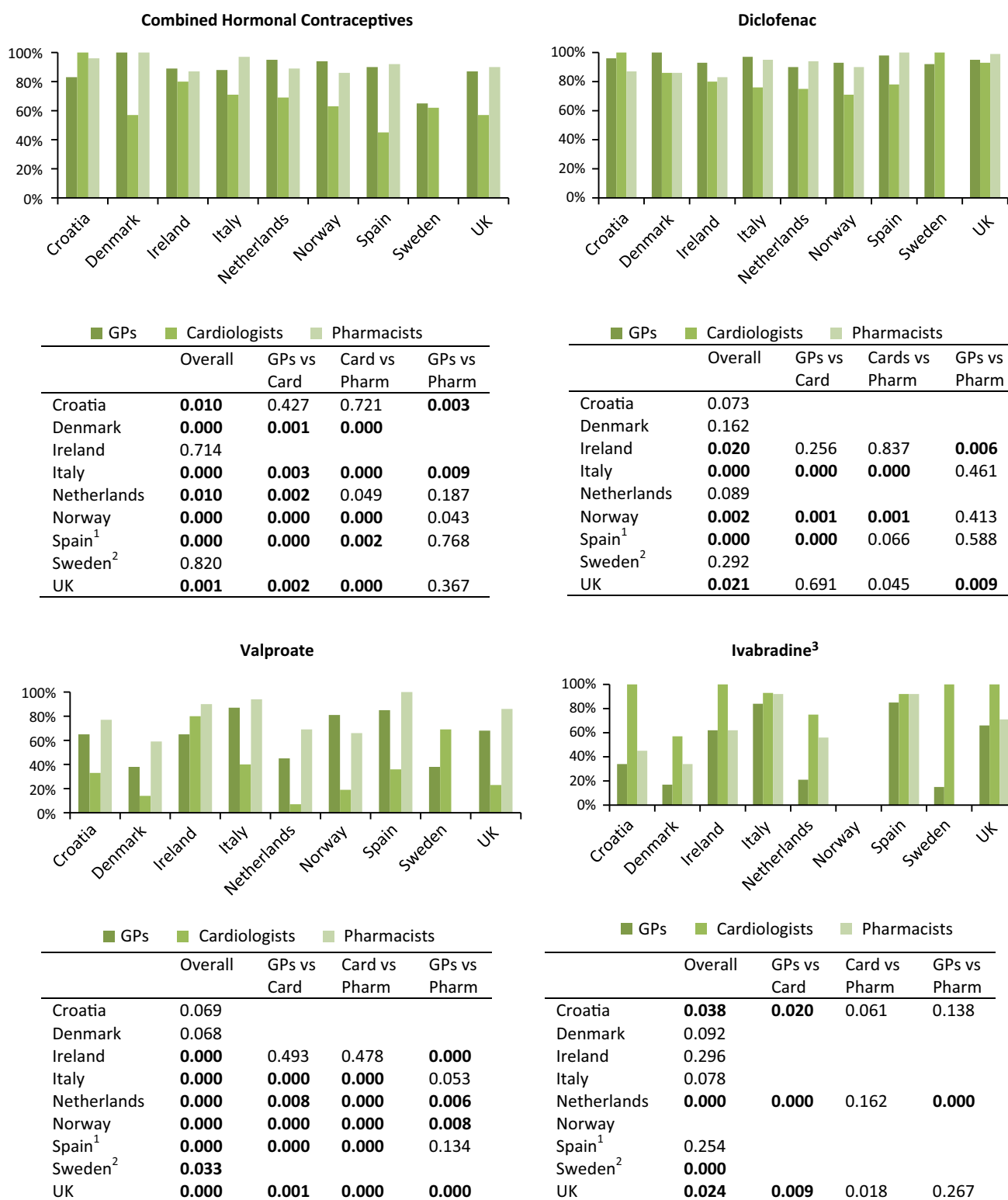


Fig. 4 Awareness of four specific safety issues by profession and *P* values for differences between professions within countries. *P* values in bold are considered statistically significant. ¹Despite not being targeted, a few pharmacists from Spain completed the survey. ²In

Sweden, pharmacists were not actively targeted and no pharmacists completed the survey. ³The ivabradine safety issue was not assessed in Norway. *Card* cardiologists, *GPs* general practitioners, *Pharm* pharmacists

cardiologists, whereas cardiologists were more aware of the ivabradine issue, which is largely expected given its use in the specialist setting only. We showed some differences between GPs and pharmacists, but these differed across the countries. DHPCs were most often mentioned by all three professions as the source through which HCPs had become aware of the safety issues, but other sources were also relevant depending on the safety issue and profession as well as the country.

A previous study conducted in the Netherlands showed differences between GPs and hospital pharmacists in their familiarity with DHPCs [6]. Our study showed a difference between GPs and pharmacists only in Italy. This previous study found that 28% of the GPs were not familiar with DHPCs compared to 14% of the GPs from the Netherlands in our study. This may imply that familiarity with DHPCs among GPs in the Netherlands has increased over the years. In general, there seems to be still room for improvement, with less than 80% of respondents in some professions reporting to be familiar with DHPCs (Croatia and Norway).

Of the four presented safety issues, GPs and pharmacists were least aware of the ivabradine issue. This lower awareness may be due to the fact that ivabradine is a newer active substance, likely to be prescribed by specialists, and authorised for a relatively narrow indication. Not surprisingly, this was the safety issue of which cardiologists were most aware. On the other hand, cardiologists were less aware of safety issues of drugs that are primarily prescribed in general practice (i.e. contraceptives and diclofenac), which is still of cause for concern since the communications referred to cardiovascular-related risks. A previous study had also shown that specialists were less aware than GPs and community pharmacists of a safety issue for a drug prescribed and dispensed in primary care [6]. An important explanation may be that DHPCs about contraceptives and diclofenac were not sent to cardiologists in all countries (Table 1). This indicates that in the evaluation of the effectiveness of safety communication strategies, awareness among the targeted professions should be assessed rather than awareness among HCPs in general. Findings, however, were not completely consistent as some professional groups received a DHPC but were less aware. Further studies should assess whether cardiologists and other specialists are also interested in receiving DHPCs about adverse effects relevant for their specialty, instead of only receiving DHPCs for drugs used to treat specialty-related diseases.

In three countries (i.e. Ireland, the Netherlands, and the UK), pharmacists were more aware of a safety issue about a drug primarily prescribed by specialists (i.e. valproate) than GPs. However, in Norway, GPs were more aware of this issue than pharmacists. There may be various reasons for this and for other observed differences across countries

in our study. One reason could be differences between countries in uptake of a certain drug and healthcare systems (e.g. whether treatment is confined to the specialised setting in clinics/hospitals or initiated/repeated by GPs). Another reason could be differences across European countries in NCAs' communication strategies. Although a previous study showed that NCAs use similar methods to communicate about drug safety issues [8], the current study showed differences across the countries in the sources through which HCPs had become aware of the specific safety issues. Moreover, there were differences between and within countries with respect to the format, the target population, and the sender of the communication about the specific safety issues (Table 1). Various factors related to these strategies, such as trust in the sender of the information, may have influenced the uptake of the information [10]. Future studies should focus more on the explanations for differences across European countries. In addition, future studies should focus on whether high awareness actually translates into improved drug utilisation and health outcomes; however, study methods other than surveys are needed for such evaluations [11]. A recent systematic review showed that in more than half of the reviewed studies evaluating the impact of regulatory interventions, administrative claims databases or electronic health records databases were used [12].

Although there is room for improving HCPs' familiarity with DHPCs, this communication tool was the most common source through which the HCPs became aware of the safety issues included in our study. Information on a website or in a newsletter was also reported as an important source for many HCPs; in some cases these are likely to be the websites and newsletters of NCAs, which are long established in some countries [8]. Interestingly, medical journals were also commonly used by cardiologists aware of the contraceptive, diclofenac, and ivabradine issues. To improve HCPs' awareness of safety issues and ultimately their actual prescribing/dispensing behaviour, it is therefore important that the strategies for safety communication should be tailored to specific professions. There may also be differences in the use of sources per country. For instance, in the Netherlands, awareness of the contraceptives and diclofenac safety issues were higher than the awareness of the valproate and ivabradine issues. This may be related to the role of "professional bodies" that were indicated in the Netherlands as an important source, and that thus may amplify safety messages from NCAs.

Interestingly, several HCPs claimed to have heard about the diclofenac safety issue via educational materials despite these materials not being disseminated for this drug safety issue. This finding indicates that HCPs may have confused the regulatory term "educational materials" with other educational activities, despite examples of educational

materials being presented within the survey for clarity, suggesting a broader interpretation of this term than the regulatory meaning.

A strength of this study is the inclusion of survey respondents from a wide range of European countries; thus it was possible to assess the associations per country. However, the study also has some limitations. One limitation relates to the use of a survey methodology which could have introduced biases such as recall bias and answering tendencies [13]. Moreover, survey answering tendencies such as socially desirable answering may differ across countries [14, 15], which could have influenced our results. Another limitation is the low statistical power in some countries due to the small sample size, particularly the low number of included cardiologists. Results should therefore be interpreted cautiously. Due to the low sample size, we did not assess the sources by profession per country, and this also limits the generalisability of the findings. Previously, we compared the GPs included in our study with the total GP population in the different countries and we observed a similar pattern in terms of age and sex distribution [8]. However, representativeness cannot be guaranteed, particularly in countries with small sample sizes. In addition, pharmacists were not actively recruited in Spain and Sweden and other specialists that would have been relevant to the specific safety issues studied (e.g. neurologists or epileptologists) were not included.

5 Conclusion

We observed high familiarity with DHPCs across all three professions; however, there were differences between professions in awareness of specific safety issues. GPs and pharmacists were more aware of the safety issues concerning contraceptives and diclofenac than cardiologists, whereas cardiologists were more aware of the ivabradine issue. Different strategies may be needed to reach specialists when communicating safety issues regarding drugs outside their therapeutic area but with risks related to their field of specialisation. Aside from DHPCs, other sources such as websites, newsletters, professional bodies, or medical journals can be relevant sources for HCPs to become aware of safety issues. Our findings suggest that NCAs should explore the use of other information sources to complement the current tools used to disseminate safety information.

Acknowledgements The healthcare professionals from Croatia, Denmark, Ireland, Italy, the Netherlands, Norway, Spain, Sweden, and the UK who responded to the survey are greatly appreciated.

Other SCOPE Work Package 6 members: J. Ahlqvist-Rastad, F. Boudier, M. Foy, J. García, J. Hearn, Y. Knudsen, L. Loughin, D. Montero, H. Samdal, and A. Wennberg.

Author Contributions All authors contributed to the development and formulation of the research question. STdV, MJMvdS, and PGMM collected data in the Netherlands; AMC in Ireland; YE, ARP, and MAMM in Spain; AC and IB in Italy; IŠ and AA in Croatia; and LM in Denmark; and the other SCOPE Work Package 6 members collected data in the other countries. STdV and MJMvdS analysed the data. All authors contributed to the interpretation of the results. STdV wrote the manuscript. MJMvdS, AMC, YE, ARP, MAMM, AC, IB, IŠ, AA, LM, PD, and PGMM reviewed and edited the manuscript. PD has been involved primarily in the development, interpretation and writing of this project. She is mentioned implicitly (like all other authors) for the first two aspects and individually mentioned for the writing part. All authors have read and approved the final manuscript.

Compliance with Ethical Standards

Ethical approval was not considered necessary for this study because of the nature of the study, in which healthcare professionals were asked to complete a survey about safety communication strategies. Participants were assured that all sensitive data would be kept confidential.

Funding The work was conducted in the context of a European Commission sponsored joint action, Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE). Any opinions, conclusions and proposals in the text are those of the authors and do not necessarily represent the views of the European Commission or national competent authorities. The survey was made possible through a tendered subcontract ITT-1301, ECM-2294.

Conflict of interest Sieta T. de Vries, Maartje J.M. van der Sar, Anna Marie Coleman, Yvette Escudero, Alfonso Rodríguez Pascual, Miguel-Ángel Maciá Martínez, Amelia Cupelli, Ilaria Baldelli, Ivana Šipić, Adriana Andrić, Line Michan, and Petra Denig have no conflicts of interest that are directly relevant to the content of this study. Peter G.M. Mol is an employee of the Dutch Medicines Evaluation Board.

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